

WHAT IS CLAIMED IS:

1 1. A method for counteracting a pathologic change in the β -adrenergic signal
2 transduction pathway, comprising administering to a mammalian subject in need an effective
3 amount of a compound capable of inhibiting TGF- β signaling through a TGF- β receptor

1 2. The method of claim 1 wherein the TGF- β receptor is a TGF β -R1 receptor
2 kinase.

1 3. The method of claim 2 wherein said compound is capable of specific binding
2 to a TGF β -R1 receptor kinase.

1 4. The method of claim 2 wherein said compounds preferentially inhibits a
2 biological activity mediated by a TGF β -R1 receptor kinase.

1 5. The method of claim 1 wherein the pathologic change is selected from the
2 group consisting of (a) a reduction in the mRNA level of a β -adrenergic receptor, (b) a
3 reduction in the number of β -adrenergic receptor binding sites, (c) TGF- β -induced down-
4 regulation of Smad3 expression, and (d) loss, in β -adrenergic sensitivity.

1 6. The method of claim 5 wherein the loss in β -adrenergic sensitivity is
2 associated with the administration of a β -adrenergic agonist.

1 7. The method of claim 6 wherein the loss in β -adrenergic sensitivity results
2 from long-term or excessive administration of a β -adrenergic agonist.

1 8. The method of claim 7 wherein the β -adrenergic agonist is selected from the
2 group consisting of procaterol, albuterol, salmeterol, formoterol, and doputamine.

1 9. The method of claim 1 wherein the pathologic change is observed in lung
2 tissue.

1 10. The method of claim 9 wherein the pathologic change results in a disease or
2 condition benefiting from the improvement of lung function.

1 11. The method of claim 10 wherein the disease or condition is a
2 bronchoconstrictive disease.

1 12. The method of claim 10 wherein the disease or condition is selected from the
2 group consisting of emphysema, chronic bronchitis, chronic obstructive pulmonary disease
3 (COPD), pulmonary edema, cystic fibrosis (CF), occlusive lung disease, acute respiratory
4 deficiency syndrome (ARDS), asthma, radiation-induced injury of the lung, and lung injuries
5 resulting from other factors, such as, infectious causes, inhaled toxins, or circulating
6 exogenous toxins, aging and genetic predisposition to impaired lung function.

1 13. The method of claim 12 wherein the mammalian subject is human.

1 14. The method of claim 13 wherein the human subject is in need of
2 bronchodilation.

1 15. The method of claim 1 wherein the pathologic change is observed in cardiac
2 tissue.

1 16. The method of claim 15 wherein the mammalian subject is human.

1 17. The method of claim 16 wherein the human subject has been diagnosed with a
2 heart disease.

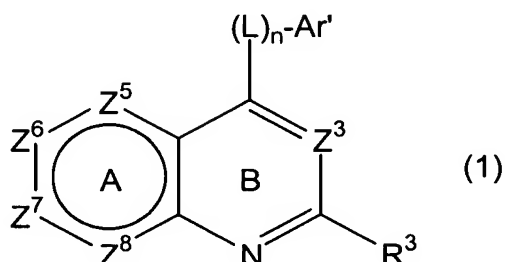
1 18. The method of claim 17 wherein the heart disease is chronic or congestive
2 heart failure (CHF).

1 19. The method of claim 3 wherein the compound is capable of binding to an
2 additional receptor kinase.

1 20. The method of claim 19 wherein the additional receptor kinase is an activin
2 receptor (Alk4).

1 21. The method of claim 2 wherein the compound is a small organic molecule.

1 22. The method of claim 21 wherein the small organic molecule is a compound of
2 formula (1)



3 or the pharmaceutically acceptable salts thereof

4 wherein R^3 is a noninterfering substituent;

5 each Z is CR^2 or N, wherein no more than two Z positions in ring A are N, and

6 wherein two adjacent Z positions in ring A cannot be N;

7 each R^2 is independently a noninterfering substituent;

8 L is a linker;

9 n is 0 or 1; and

10 Ar' is the residue of a cyclic aliphatic, cyclic heteroaliphatic, aromatic or
11 heteroaromatic moiety optionally substituted with 1-3 noninterfering substituents.

1 23. The method of claim 22 wherein the compound is a quinazoline derivative.

1 24. The method of claim 23 wherein wherein Z^3 is N; and Z^5 - Z^8 are CR^2 .

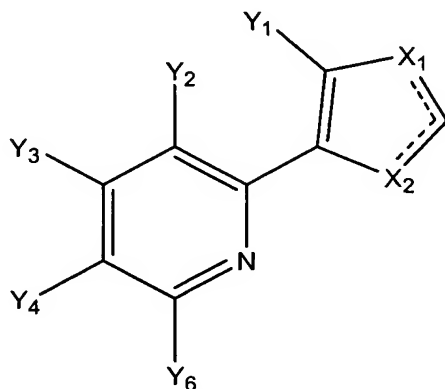
1 25. The method of claim 23 wherein Z^3 is N; and at least one of Z^5 - Z^8 is nitrogen.

1 26. The method of claim 23 wherein R^3 is an optionally substituted phenyl moiety

1 27. The method of claim 26 wherein R^3 is selected from the group consisting of
2 2-, 4-, 5-, 2,4- and 2,5-substituted phenyl moieties.

1 28. The method of claim 27 wherein at least one substituent of the phenyl moiety
2 is an alkyl(1-6C), or halo.

1 29. The method of claim 21, wherein the small organic molecule is a compound of
2 formula (2)

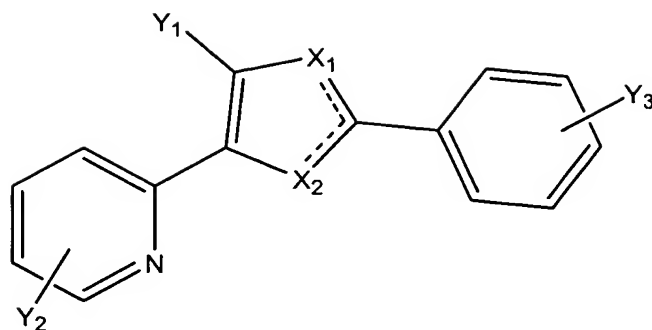


3 wherein Y₁ is phenyl or naphthyl optionally substituted with one or more substituents
4 selected from halo, alkoxy(1-6 C), alkylthio(1-6 C), alkyl(1-6 C), haloalkyl (1-6C), -O-
5 (CH₂)_m-Ph, -S-(CH₂)_m-Ph, cyano, phenyl, and CO₂R, wherein R is hydrogen or alkyl(1-6 C),
6 and m is 0-3; or phenyl fused with a 5- or 7-membered aromatic or non-aromatic ring
7 wherein said ring contains up to three heteroatoms, independently selected from N, O, and

8 Y₂, Y₃, Y₄, and Y₅ independently represent hydrogen, alkyl(1-6C), alkoxy(1-6 C),
9 haloalkyl(1-6 C), halo, NH₂, NH-alkyl(1-6C), or NH(CH₂)_n-Ph wherein n is 0-3; or an
10 adjacent pair of Y₂, Y₃, Y₄, and Y₅ form a fused 6-membered aromatic ring optionally
11 containing up to 2 nitrogen atoms, said ring being optionally substituted by one or more
12 substituents independently selected from alkyl(1-6 C), alkoxy(a-6 C), haloalkyl(1-6 C), halo,
13 NH₂, NH-alkyl(1-6 C), or NH(CH₂)_n-Ph, wherein n is 0-3, and the remainder of Y₂, Y₃, Y₄,
14 and Y₅ represent hydrogen, alkyl(1-6 C), alkoxy(1-6C), haloalkyl(1-6 C), halo, NH₂, NH-
15 alkyl(1-6 C), or NH(CH₂)_n-Ph wherein n is 0-3; and

16 one of X₁ and X₂ is N and the other is NR₆, wherein R₆ is hydrogen or alkyl(1-6 C)

1 30. The method of claim 21 wherein said small organic molecule is a compound
2 of formula (3)

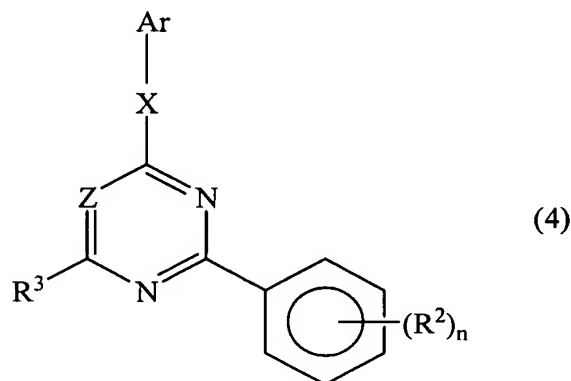


wherein Y_1 is naphthyl, anthracenyl, or phenyl optionally substituted with one or more substituents selected from the group consisting of halo, alkoxy(1-6 C), alkylthio(1-6 C), alkyl(1-6 C), $-O-(CH_2)_n-Ph$, $-S-(CH_2)_n-Ph$, cyano, phenyl, and CO_2R , wherein R is hydrogen or alkyl(1-6 C), and n is 0, 1, 2, or 3; or Y_1 represents phenyl fused with an aromatic or non-aromatic cyclic ring of 5-7 members wherein said cyclic ring optionally contains up to two heteroatoms, independently selected from N, O, and S;

Y_2 is H, $NH(CH_2)_n-Ph$ or $NH-alkyl(1-6\ C)$, wherein n is 0, 1, 2, or 3;

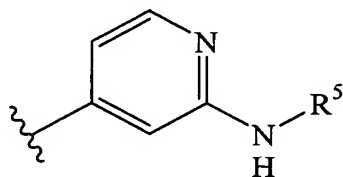
Y_3 is CO_2H , $CONH_2$, CN, NO_2 , alkylthio(1-6 C), $-SO_2-alkyl(C1-6)$, alkoxy(C1-6), $SONH_2$, $CONHOH$, NH_2 , CHO, CH_2NH_2 , or CO_2R , wherein R is hydrogen or alkyl(1-6 C); one of X_1 and X_2 is N or CR' , and other is NR' or CHR' wherein R' is hydrogen, OH, alkyl(C-16), or cycloalkyl(C3-7); or when one of X_1 and X_2 is N or CR' then the other may be S or O.

31. The method of claim 21 wherein said small organic molecule is a compound of formula (4)



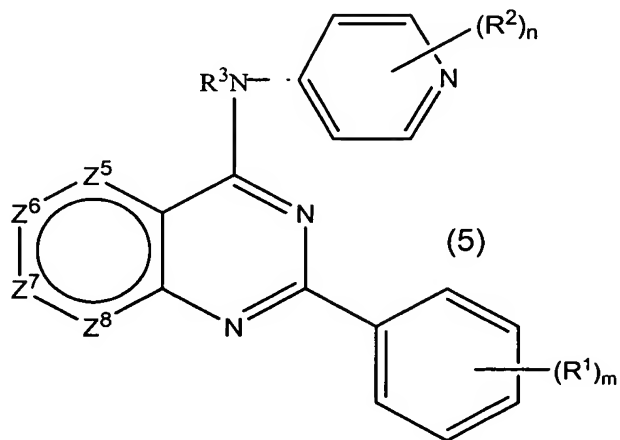
and the pharmaceutically acceptable salts and prodrug forms thereof; wherein

4 Ar represents an optionally substituted aromatic or optionally substituted
 5 heteroaromatic moiety containing 5-12 ring members wherein said heteroaromatic moiety
 6 contains one or more O, S, and/or N with a proviso that the optionally substituted Ar is not



7 wherein R⁵ is H, alkyl (1-6C), alkenyl (2-6C), alkynyl (2-6C), an aromatic or
 8 heteroaromatic moiety containing 5-11 ring members;
 9 X is NR¹, O, or S;
 10 R¹ is H, alkyl (1-8C), alkenyl (2-8C), or alkynyl (2-8C);
 11 Z represents N or CR⁴;
 12 each of R³ and R⁴ is independently H, or a non-interfering substituent;
 13 each R² is independently a non-interfering substituent; and
 14 n is 0, 1, 2, 3, 4, or 5. In one embodiment, if n>2, and the R²'s are adjacent, they can
 15 be joined together to form a 5 to 7 membered non-aromatic, heteroaromatic, or aromatic ring
 16 containing 1 to 3 heteroatoms where each heteroatom can independently be O, N, or S.

1 32. A method of claim 21 wherein said small organic molecule is a compound of
 2 formula (5)



3 or the pharmaceutically acceptable salts thereof;
 4 wherein each of Z⁵, Z⁶, Z⁷ and Z⁸ is N or CH and wherein one or two Z⁵, Z⁶, Z⁷ and
 5 Z⁸ are N and wherein two adjacent Z positions cannot be N;

6 wherein m and n are each independently 0-3;
7 wherein two adjacent R¹ groups may be joined to form an aliphatic heterocyclic ring
8 of 5-6 members;
9 wherein R² is a noninterfering substituent; and
10 wherein R³ is H or CH₃.

1 33. A method for counteracting decline in β -adrenergic receptor sensitivity,
2 comprising administering to a mammalian subject in need an effective amount of a
3 compound capable of inhibiting TGF- β signaling through a TGF- β receptor.

1 34. The method of claim 33 wherein the decline in β -adrenergic receptor
2 sensitivity is agonist-induced.

1 35. The method of claim 34 wherein the loss in β -adrenergic receptor sensitivity
2 results from one or more causes selected from the group consisting of agonist-induced
3 uncoupling, sequestration, degradation and desensitization of a β -adrenergic receptor.

1 36. The method of claim 33 wherein the loss in β -adrenergic receptor sensitivity is
2 due to an agonist-independent mechanism.

1 37. The method of claim 36 wherein the mammalian subject is human.

1 38. The method of claim 37 wherein the human subject is in need of
2 bronchodilation.

1 39. The method of claim 38 wherein the human subject has been diagnosed with a
2 disease or condition benefiting from the improvement of lung function.

1 40. The method of claim 39 wherein the disease or condition benefiting from the
2 improvement of lung function is selected from the group consisting of emphysema, chronic
3 bronchitis, chronic obstructive pulmonary disease (COPD), pulmonary edema, cystic fibrosis,
4 occlusive lung disease, acute respiratory deficiency syndrome (ARDS), asthma, radiation-

5 induced injury of the lung, lung injuries resulting from infectious causes, inhaled toxins, or
6 circulating exogenous toxins, aging and genetic predisposition to impaired lung function.

1 41. The method of claim 39 wherein the disease or condition benefiting from the
2 improvement of lung function involves acute lung injury.

1 42. The method of claim 39 wherein the disease or condition benefiting from the
2 improvement of lung function is unaccompanied by lung fibrosis.

1 43. The method of claim 39 wherein the disease or condition benefiting from the
2 improvement of lung function is at a stage when lung fibrosis is not a major symptom.

1 44. The method of claim 39 wherein the disease or condition benefiting from the
2 improvement of lung function is associated with inflammation of the lungs.

1 45. The method of claim 39 wherein the disease or condition benefiting from the
2 improvement of lung function is associated with abnormal inflammatory response of the
3 lungs to noxious particles or gases.

1 46. The method of claim 39 wherein the disease or condition benefiting from the
2 improvement of lung function is chronic obstructive pulmonary disease (COPD).

1 47. The method of claim 39 wherein the human subject is treated with a β -
2 adrenergic agonist.

1 48. The method of claim 47 wherein the β -adrenergic receptor is a β 2-adrenergic
2 receptor.

1 49. The method of claim 48 wherein the β 2-adrenergic agonist is a bronchodilator.

1 50. The method of claim 48 wherein the β 2-adrenergic agonist is selected from the
2 group consisting of procaterol, albuterol, salmeterol, and formoterol.

1 51. The method of claim 37 wherein the mammalian subject has been diagnosed
2 with a heart disease.

1 52. The method of claim 52 wherein the heart disease is congestive heart failure.

1 53. The method of claim 52 wherein the administration of the compound capable
2 of inhibiting TGF- β signaling through a TGF- β receptor results in increased ionotropy.

1 54. The method of claim 52 wherein the administration of the compound capable
2 of inhibiting TGF β signaling through a TGF β receptor results in decrease in circulating
3 catecholamines.

1 55. The method of claim 52 wherein the administration of the compound capable
2 of inhibiting TGF β signaling through a TGF β receptor results in decreased arrhythmia and
3 peripheral vasoconstriction.

1 56. The method of claim 52 wherein the human subject is treated with brain-
2 derived natriuretic peptide (BNP).

1 57. The method of claim 33 wherein said receptor is a TGF β -R1 receptor kinase.

1 58. The method of claim 57 wherein the compound capable of inhibiting TGF- β
2 signaling through said TGF β -R1 receptor kinase is administered concurrently with treatment
3 with a compound resulting in a loss in β -adrenergic receptor sensitivity.

1 59. The method of claim 57 wherein the compound capable of inhibiting TGF β
2 signaling through said TGF β -R1 receptor kinase is administered intermittently with treatment
3 with a compound resulting in a loss in β -adrenergic receptor sensitivity.

1 60. The method of claim 57 wherein the compound capable of inhibiting TGF β
2 signaling through said TGF β -R1 receptor kinase is administered following treatment with a
3 compound resulting in desensitization of a β -adrenergic receptor.

1 61. A method for selective inhibition of β 2-adrenergic receptor (β 2-AR)
2 expression and response to a β -adrenergic receptor antagonist, comprising treating a cell
3 expressing said β 2-AR with a compound capable of TGF- β signaling through a TGF- β
4 receptor.

1 62. The method of claim 61 wherein the TGF- β receptor is a TGF β -R1 kinase.

1 63. The method of claim 62 wherein the cell is a cardiac cell.

1 64. The method of claim 63 wherein the cardiac cell is diseased.

1 65. The method of claim 64 wherein the cardiac cell is that of a subject having
2 congestive heart failure (CHF).